e. returning the antibody-contacted plasma to the patient.

18. The method of claim 17, wherein the antibody is immobilized in a solid support or membrane.

19. The method of claim 17, wherein the antibody is recombinant or a binding fragment.

20. The method of claim 17, wherein the antibody is a mixture of antibodies immunoreactive with the targeted immune system inhibitor .

21. The method of claim 17, wherein the patient is human.

22. The method of claim 17 wherein the targeted immune system inhibitor is selected from the group consisting of soluble receptors for tumor necrosis factors alpha and beta.

Remarks

Amendment to Priority

The specification has been amended so that the revised priority claim is now found on page 1 of the application.

Objections to Specification and Rejections under 35 U.S.C. 112, second paragraph

The reference to "tissue necrosis factor" has been replaced with "tumor necrosis factor" on page 3 of the specification and in claim 7. The definitions for the abbreviations have been inserted into claims 1 and 11.

The phrase "molecule binding to soluble cytokine receptor molecules" has been replaced with "antibody" and claim 4 defining the molecule as an antibody cancelled.

The word "receptor" has been inserted after "cytokine".

"Reduced in amount" has been stated to be relative to the levels prior to treatment.

Claim 1 has also been amended to refer to reducing the amount of transformed, infected or diseased tissue, rather than inducing an immune response, to make the preamble consistent with the method steps.

Serial No.: 09/709,045
Filed: November 10, 2000
AMENDMENT

Claims 1, 4, 6, 8 and 11 were rejected under 35 U.S.C. 112, first paragraph, as lacking written description and requiring undue experimentation for GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF, and SCF. This rejection is believed to be without merit, but these embodiments have been cancelled from the claims solely to facilitate prosecution at this time.

With respect to the examiner's comment regarding the efficacy with respect to removal of soluble TNFR1 and soluble TNFR2, the examiner is using an improper legal standard. It is well established that no examples are required. It is also well established that the standard is not the same as what might be required to convince the FDA. In this case, applicant has conducted further clinical trials in Europe at the Klinik-At-Georg and has data showing efficacy in a number of patients, with the following results: 50% or greater tumor reductions were observed in 4/4 patients with metastatic breast cancer, 2 of 2 patients with metastatic prostate cancer, 1 of 1 patient with metastatic colon cancer, and 1 of 1 patient with metastatic non-small cell carcinoma of the lung. These patients were treated using a Sepharose column having coupled thereon rabbit polyclonal antibody to human sTNFR1 and sTNFR2.

The examiner's attention is again drawn to U.S. Patent No. 6,379,708 which claims the same subject matter. This is noted as further evidence of enablement and patentability of the claims under 35 U.S.C. 112. Applicant requests declaration of an interference with respect to this patent, which claims the same subject matter. It is suggested that new claim 17 be used as the count. Applicant should be senior party, having an effective priority date of May 22, 1998.

Serial No.: 09/709,045
Filed: November 10, 2000
AMENDMENT

New Claims

New claims 17-22 have been added, which essentially correspond to U.S. Patent No. 6,379,708 to Howell, et al. This application claims priority to U.S.S.N. 09/083,307 filed May 22, 1998, before the earliest filing date of the Howell patent.

The basis for the new claims is indicated in the claims as shown below in bold. The basis as found in Applicant's May 22, 1998, application is also shown below in italics.

17. A method of enhancing an immune response in a patient **(page 1, lines 6-7)** comprising:

a. obtaining whole blood from the patient **(page 18, lines 4-8)**; *(page 6)*

b. separating out the plasma. **(page 18, lines 7-8)**; *(page 6)*

c. contacting the plasma with antibody specifically binding to a targeted immune system inhibitor **(page 18, lines 8-11; page 6, lines 1-7)**; *(page 11, lines 23-26)*

d. removing the inhibitor bound to the antibody from the plasma **(page 18, line 8-11)**; *(page 11, lines 23-26)* and

e. returning the antibody-contacted plasma to the patient. **(page 18, lines 11-15)**. *(page 7)*

18. The method of claim 17, wherein the antibody is immobilized in a solid support or membrane. **(page 9, lines 1-5)** *(page 11, lines 27-28)*

19. The method of claim 17, wherein the antibody is recombinant or a binding fragment. **(page 6, lines 18-20)**. *(page 11, lines 24-26)*

20. The method of claim 17, wherein the antibody is a mixture of antibodies immunoreactive with the targeted immune system inhibitor. **(page 6, line 27)** *(page 11, lines 22-29)*

Serial No.: 09/709,045
Filed: November 10, 2000
AMENDMENT

21. The method of claim 17, wherein the patient is human. **(page 6, line 26).** *(examples)*

22. The method of claim 17 wherein the targeted immune system inhibitor is selected from the group consisting of soluble receptors for tumor necrosis factors alpha and beta. *(page 11, lines 22-29)*

Double Patenting Rejection

The claims in U.S. Patent No. 6,231,536 were interpreted by the examiner as requiring removal of the soluble tissue necrosis factor receptor using a molecular weight exclusion. There is nothing in such an interpretation that would make obvious the method as currently claimed. To the extent this rejection is maintained, it is respectfully requested that a final determination not be made until the outcome of the above-requested interference becomes available.

Allowance of claims 1-3, 5, 6, 8-11 and 17-22 and declaration of an interference with U.S. patent No. 6,379,708 is respectfully requested.

Respectfully submitted,

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Serial No.: 09/709,045
Filed: November 10, 2000
AMENDMENT

CERTIFICATE OF FACSIMILE TRANSMITTAL

I hereby certify that this correspondence and any document referred to as being included therein is being facsimile transmitted to the Patent and Trademark Office onJanuary 22, 2003.

Patrea Pabst

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APPENDIX: Marked up Copy of Amended Claims

1. (amended) A method for [inducing an immune response against] reducing the amount of transformed, infected or diseased tissue in a patient comprising

contacting the blood of a patient in need thereof with an effective amount of [a molecule] antibodies binding to soluble cytokine receptor molecules, wherein the cytokine receptor is selected from the group consisting of [GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF] soluble tumor necrosis factor receptor-1 ("sTNFR-1") and soluble tumor necrosis factor receptor-2 ("sTNFR-2") wherein binding of the [molecule] antibodies prevents the soluble cytokine receptor from binding to the cytokine, until the transformed, infected, or diseased tissue is reduced in amount compared to the amount present at the time the treatment is initiated.

2. The method of claim 1 wherein the tissue is a solid tumor.

3. The method of claim 1 wherein the disease is a viral or parasitic disease causing immunosuppression.

5. The method of claim 1 further comprising treating the tissue with an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation.

6. The method of claim 1 further comprising selectively removing soluble cytokine receptor molecules.

8. (amended) The method of claim [7] 1 wherein the cytokine receptor molecules are removed by binding to the cytokine or to an antibody or antibody fragment immunoreactive with the cytokine receptor molecules.

9. The method of claim 8 wherein the cytokine or antibody or antibody fragments are immobilized in a filter or column through which the patient's blood or plasma is circulated prior to being returned to the patient.

10. (amended) The method of claim [4] 1 wherein the antibody is humanized.

11. (twice amended) The method of claim 1 comprising

contacting the blood or components thereof with [molecules binding to soluble cytokine receptor molecules, wherein the cytokine is selected from the group consisting of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF, wherein binding of the molecule prevents the soluble cytokine receptor from binding to the cytokine, in an amount effective to reduce the amount of transformed, infected, or diseased tissue, wherein the molecules are in a pharmaceutically acceptable, endotoxin free carrier or] antibodies or antibody fragments immobilized in a sterile endotoxin free extracorporeal device.

17. A method of enhancing an immune response in a patient comprising:

a. obtaining whole blood from the patient;

b. separating out the plasma;

c. contacting the plasma with antibody specifically binding to a targeted immune system inhibitor;

d. removing the inhibitor bound to the antibody from the plasma ; and

e. returning the antibody-contacted plasma to the patient.

18. The method of claim 17, wherein the antibody is immobilized in a solid support or membrane.

19. The method of claim 17, wherein the antibody is recombinant or a binding

fragment.

20. The method of claim 17, wherein the antibody is a mixture of antibodies immunoreactive with the targeted immune system inhibitor .

21. The method of claim 17, wherein the patient is human.

22. The method of claim 17 wherein the targeted immune system inhibitor is selected from the group consisting of soluble receptors for tumor necrosis factors alpha and beta.

METHOD AND SYSTEM TO REMOVE CYTOKINE INHIBITOR IN PATIENTS

Background of the Invention

The present invention is generally in the field of enhancing an immune response, and particularly relates to the removal of TNF inhibitors in a patient, such as a cancer patient, to promote inflammation and thereby induce remission of the cancer.

This application claims priority to U.S.S.N. 09/699,003 filed October 26, 2000, which is a continuation of U.S.S.N. 09/316,226 filed May 21, 1999, now U.S. Patent NO. 6,231,536, which claims priority to U.S.S.N. 09/083,307 filed May 22, 1998, and to U.S.S.N. 60/164,695 filed November 10, 1999.

Conventional cancer therapy is based on the use of drugs and/or radiation which kills replicating cells, hopefully faster than the agents kill the patient's normal cells. Surgery is used to reduce tumor bulk, but has little impact once the cancer has metastasized. Radiation is effective only in a localized area.

The treatments can in themselves kill the patient, in the absence of maintenance therapy. For example, for some types of cancer, bone marrow transplants have been used to maintain the patient following treatment with otherwise fatal amounts of chemotherapy. Efficacy has not been proven for treatment of solid tumors, however. "Cocktails" of different chemotherapeutic agents and combinations of very high doses of chemotherapy with restorative agents, for example, granulocyte macrophage colony stimulating factor ("GM-CSF"), erythropoietin, thrombopoetin, granulocyte stimulating factor, ("G-CSF"), macrophage colony stimulating factor ("M-CSF") and stem cell factor ("SCF") to restore platelet and white cell levels, have been used to treat aggressive cancers. Even with the supportive or restrictive therapy, side effects are severe.

Summary of the Invention

A method to treat disorders characterized by production of soluble TNF receptors, such as many types of cancer, and certain diseases such as HIV, where the disease immunosuppresses the patient, has been developed. Antibodies which bind to TNF receptor, including the soluble TNF receptor, are administered to the patient in an amount effective to neutralize the molecules which block binding of TNF to the receptor, thereby inducing inflammation. In the preferred embodiment, the patient's blood is passed through a column having antibodies immobilized thereon, which bind to and remove the soluble TNF receptor molecules. The process can be performed alone or in combination with other therapies, including radiation, chemotherapy (local or systemic, for example, treatments using alkylating agents, doxyrubicin, carboplatinum, cisplatinum, and taxol, and other drugs which may be synergistic in effect with "unblocked" cytokines: or anti-angiogenic factors. Antibodies may be utilized which are immunoreactive with one or more of the following:

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[tissue] tumor necrosis factor receptor-1 ("TNFR-1"), [tissue] tumor necrosis factor receptor-2 ("TNFR-2"), interleukin-2 receptor ("IL-2R"), interleukin-1 receptor ("IL-1R"), interleukin-6 receptor ("IL-6R"), or interferon-gamma receptor ("sIFN-gammaR"). The patient is preferably treated daily for at least three weeks, diagnostic tests conducted to verify that there has been shrinkage of the tumors, then the treatment regime is repeated as needed.

Detailed Description of the Invention

Innate, natural and antigen specific killer mechanisms represent the best arsenal for dealing with melanoma cells *in vitro* and *in vivo*. Central to these cellular destructive mechanisms is tumor necrosis factor (TNF-α), an inflammatory cytokine produced by macrophages and earlier mononuclear cells and TNF-β, a related cytokine produced and secreted by killerT-lymphocytes with highly selective antigen specific receptors, Old L.J., Antitumor activity of

such as a virus like HIV or parasite. The neutralizing agent is typically an antibody reactive with the receptor. the antibodies will typically be reactive with both the soluble and immobilized forms of the receptor. These include soluble tumor necrosis factor receptor ("sTNF-R"), soluble interleukin-2 receptor ("sIL-2R"), soluble interleukin-1 receptor ("sIL-1R"), soluble interleukin-6 receptor ("sIL-6R"), or soluble interferon-gamma receptor ("sIFN-gammaR"). The advantage of selective removal or neutralization is that the same beneficial effect is obtained in treatment of the disorder but the treatment is much less expensive and safer since exogenous plasma or albumin does not have to be administered to the patient when there is selective removal, as in the case of ultrapheresis and the cytotoxic effects of radiation and chemotherapy are avoided.

The receptors can be removed by binding to the cytokine, an epitope thereof, or an antibody to the receptor. The antibodies to the receptors can be immobilized in a filter, in a column, or using other standard techniques for binding reactions to remove proteins from the blood or plasma of a patient, or administered directly to the patient in a suitable pharmaceutically acceptable carrier such as saline. As used herein, antibody refers to antibody, or antibody fragments (single chain, recombinant, or humanized), immunoreactive against the receptor molecules. In the most preferred embodiment, the antibody is reactive with the carboxy-terminus of the shed receptor molecules, thereby avoid concerns with signal transduction by the receptor is still present on the cell surface.

Antibodies can be obtained from various commercial sources such as Genzyme Pharmaceuticals. These are preferably humanized for direct administration to a human, but may be of animal origin if immobilized in an extracorporeal device. Antibodies may be monoclonal or polyclonal. The